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Presidential Address: Physiological Genetics—Who Needs It?[1]

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Turn up my metaphors and do not fail,
There if you seekest them, such things to find
As will be helpful to an honest mind

[John Bunyan, *Pilgrim's Progress* (as adapted by Vaughan Williams)]

The American Society of Human Genetics holds an annual meeting and has a new president every year. One incumbent (Ruddle 1985) compared the office to a butterfly, with a brief and glorious opportunity for flight; another (Rosenberg 1981), to a salmon exhausted by the business expected of it. I tend to think of the butterfly's precursor—the one that creeps before it soars; and I appreciate the prespawning salmon who seldom leaps. Members of this society are not butterflies, salmon, or whatever soars and leaps; but our activities might be analogous. For the most part, they take place at a quiet level, as the necessary antecedents for those flights—by some of us—that are noticed. Milton said that "they also serve who only stand and wait," and so it is with our members, in the most part; for without caterpillars there are no butterflies; and without members, no society.

The trajectory of these thoughts implies that our society is evolving. To understand where we are going, it is helpful to know from where we have come. Human genetics is changing; on this fact most will agree. Its progress involves arrays of concepts and methods, both new and traditional, and a knowledge base, much of it new and increasing rapidly, as witnessed at this meeting. Along with human biology in general, human genetics has no aspect impervious to the techniques of molecular genetics. Because we change in what we do, we are making history. History is the study of change. Accordingly, as

[1] This article is a slightly modified version of the address delivered on November 3, 1986, in Philadelphia at the annual meeting of the American Society of Human Genetics.

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many did before me, I surveyed previous presidential addresses to this society and I found there the expected evidence of change over more than 3 decades. Although I found only 18 published lectures (there are no records of the society to explain why more than half the presidents did not publish an address—is there not an opportunity here for an archival activity?), the lectures are an interesting and diverse record of human genetics in its various guises. I found something else to ponder: the time allotted to the presidential address on the program of the annual meeting has apparently decreased as the scientific program has increased. Perhaps we can anticipate a meeting in the future when there will be no room for a speech from a prepensioner, presumably because contributions by the members and their guests have displaced all else. There is another extrapolation: while the importance of the corporate body is increasing, that of individual members may be decreasing; but if human genetics has become of greater concern to society at large, the responsibility of the individual member is commensurately greater. I will return to this idea.

HIERARCHIES

Geneticists are biologists. Rutherford is said to have held biologists in low regard, likening us to postage-stamp collectors. That unflattering hierarchical viewpoint was not limited to a physicist's view of biologists. There was a corresponding in-house hierarchy among a subset of human biologists. For example, Garrod, in one of his honorary lectures Garrod (1924), referred to the contemporary ranking of prestige in the medical profession. The physician belonged to a lower caste, and persons with inclinations to the laboratory sciences considered themselves to be in a higher category. Garrod deplored this situation, believing that we need scientists of all types to understand human biochemical individuality and interpret its role in susceptibility to disease. Little has changed with time. Even now, among human geneticists, there is a subtle caste system, the ranking unchanged since Garrod's time. Our molecular colleagues are the Brahmins, and others are in some lower order. One can understand why this is so, but if we return to a metaphor that I used earlier, the caterpillars are necessary for the butterflies—and vice versa.

The reductive approach of molecular genetics appeals strongly, and it is one explanation, powerful to be sure, for some aspects of biological variation. It is also easier to be reductive than holistic when faced with the phenomenon of life or, more specifically, when trying to understand the significance of human variation. Biological order is not the statistical order in the periodic crystal of chemistry. DNA, which is the aperiodic crystal manipulated by molecular geneticists, is a source of conferred order at the level of the whole living organism. To know how that happens is the real challenge in biology today. Physiological genetics attempts to meet that challenge. Of course, there is a contradiction of terms here in that physiology is the integrative study of homeostatic systems and genetics is the reductive discipline dedicated to the components of the systems.

The reductionist approach distinguishes between the basic principles governing the elements of structure and the properties of the whole structure—and is

devoted to the former. At the same time, we understand that the organism can be known only by studying it when it is whole, assuming that the basic principles need not be questioned. However, there is an uncertainty principle here. We cannot understand the organism if we do not know its parts; but in knowing the parts we may have lost the organism. It is an old problem in biology—designated earlier as the phenomenon of "emergence" (Mayr 1982, pp. 63–64), by which it was meant that the new characteristics of the whole system cannot be deduced from knowledge of its components.

The living organism is an open thermodynamic system whose components exhibit oscillating steady states, with local equilibrium conditions, in a far-from-equilibrium system. It is a dissipative structure, meaning that maintenance of the structure requires continuous input of energy while the effect of structure is to dissipate the energy. It is also a controlled system. Integration of the parts controls the flow of energy from moment to moment—and thus its properties at any moment—and it also determines development from simpler to more complex stages of its structure. We know that while genes are one of the determinants of both the development and the functions of dissipative structures, they are not the only ones; and we do not yet know well enough how the parts interact to achieve the whole. That is a goal of the cell biologists.

The potential for discordance between reductionist and holistic approaches is brought home by some recent experiments that might be called purposeful tinkering. When pieces of foreign genomic DNA, whether expressed or not, are inserted randomly by transgenic techniques into the nuclear genome of a germ cell, they can become insertional mutagens causing reduced viability (Wagner et al. 1983) and dysmorphic effects (Woychik et al. 1985) in the organism. Such consequences tell us that there is more to know about the precision of insertion; about the number, order, and place of genes on chromosomes; and about the role of nucleotide sequences adjacent to transcribed genes.

These are not unusual thoughts; they are simple, obvious ones—and their utterance here is tolerated because of the occasion. Nonetheless, I am addressing a membership that has a hierarchical value according to subspeciality. Rather than rank ourselves on a ladder with rungs above and below in the style of pre-Darwinian naturalists, or on a branching tree as did Darwin, I suggest that we could be seen collectively as a pyramid with a polygonal base (fig. 1), the corners representing some of our principal interests, our most numerous affiliations forming the base; at the top is physiological genetics. This ordering of relationships is meant to imply that (1) all activities are necessary for the structure and (2) the majority take place at ground level.

TAXONOMY[2]

As molecular genetics increases the knowledge base of biology, there is a new opportunity for an old exercise. I refer to systematics or taxonomy. A

[2] Slides of subheadings were prepared at the last moment and used during the address to help listeners to follow the themes. This slide was a distraction! Two very large projections, on screens to each side of and behind me, presented the audience with the unusual word "TAXANOMY." Later, I received advice on spelling and typing.

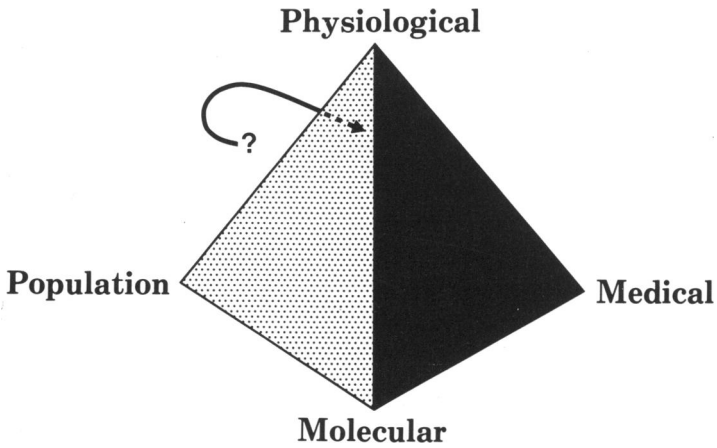

FIG. 1.—Human genetics (and biology) as an edifice. Activities (disciplines) necessary for its construction are indicated. The unnamed activity is readers' choice. Physiological genetics is attained by building the edifice.

week does not pass without a report somewhere describing a cloned human DNA sequence (Schmidtke et al. 1986). It is either the report of a new sequence or a new report on an old sequence. At the end of 1986, which will be the tenth anniversary of the first cloned human gene (the one for chorionic somatomammotropin), it is said there will be more than 2,500 published reports describing more than 500 different human gene sequences. Among the articles are at least 35 independent reports of cloned β-globin genes, the majority reporting alleles associated with disease. Growth of this knowledge at such a high rate is likely to continue during the next decade. Are there implications in this for our society? I see at least two; one concerns data bases and information systems, the other genomics. Both are forms of taxonomy.

Data Bases and Information Science

Our tradition is to use printed periodicals for depositing and disseminating information. Peer-generated newsletters fill gaps in fast-moving fields. Better still are electronic data bases, to keep pace with the growth of knowledge. For example, for the human genome, the Yale group has integrated data bases covering published literature, existence and source of cloned sequences for use as probes, polymorphic restriction sites, assignments of loci to chromosomes, and comparative maps for mouse and man. These files are the offspring of the biannual Human Genome Mapping Workshops. A new set of data bases will be established in Europe for the 1987 workshop, and the Paris and Yale files will be electronically compatible. Steps are being taken to enable geneticists at other locations to obtain such information systematically and to use it for their

own research or in genetic counseling (Scriver 1985). There will be editorial control of entries, with revision and correction of existing entries as necessary.

The information science required for this endeavor is already considerable, and it will expand with adaptations to the new technologies such as compact and video discs, computers with capacity for parallel processing, artificial intelligence, and so on. Is there any real doubt that the data bases are relevant and necessary? Whether they are sufficient is the issue.

The National Academy of Sciences (USA) has issued an interesting report in this context (National Academy of Sciences 1985). It came in response to a concern that we are at "a point in the history of biology where new generalizations of higher order biological laws are being approached but may be obscured by the simple mass of data." To have a clear picture is important because "in every hierarchical level from atoms to ecosystems, common hardware, common programs, and common strategies are used to achieve diverse ends" (Holden 1985). Since we human geneticists believe that there is unity in diversity, we are interested in data bases of homologies and analogies in biological systems. We need, as it were, an electronic thesaurus to deal with synonymous parts in context, carry out searches, and do cross-referencing.[3] The National Academy of Sciences suggests that we should begin now to develop a biology-wide information system, a matrix data base computerized and structured for access in multiple categories including organizational complexity from atoms to populations, phenotypes to phylogenetic status, molecules to mental processes, and so on (Holden 1985). I suspect that there will have to be more interplay between the biological characteristics being cataloged and the formal information sciences called on to do the job. Some of that interplay is already in progress, for example in the Molecular Biology Computer Research Resource at Harvard, at GenBank in Los Alamos, in the data bank at the European Molecular Biology Laboratory in Heidelberg, and at the repository of cloned human DNA probes established by the American Type Culture Collection.

The scientists who develop such data bases are in a different category from those who are developing the data—neither higher nor lower, just different. The former have skills both in biology and in information science; their data bases allow us to search for "general laws and structures . . . [and they] will make general biology much more accessible to the biomedical scientists" (National Academy of Sciences 1985). A data base of data bases is a feasible point of departure from which to begin a major taxonomy of biological systems (Holden 1985).

In the meantime, there are initiatives in our own area of human genetics. Groups already mentioned are keeping track of the human genome map. The Los Alamos laboratory has a repository of sorted chromosomes and the DNA

[3] I am grateful to George Cahill, vice-president, Howard Hughes Medical Institute, who shared correspondence on the thesaurus concept from Temple F. Smith, director, Molecular Biology Computer Research Resources, Dana-Farber Cancer Institute, Harvard Medical School. See also other articles and annotations: B. T. Foley, D. Nelson, M. T. Smith, and C. Burks. 1986. Trends Genet. **2**:233–238; Hamn, G., and G. Cameron. 1986. Nucleic Acids Res. **14**:5–9; and Felix, G., and W. S. Badman. 1986. Science **231**:203.

sequence registry (GenBank). The National Institute of Child Health and Human Development, under contract with the American Type Culture Collection, has established the repository of human cloned DNA segments. Dedicated persons on behalf of this society (Beaudet 1985) and others in Europe (Cooper and Schmidtke 1986) maintain directories of cloned human DNA sequences for diagnosis of human disease. There are geneological registers of Amish, Mormon, Mexican-American, and French-Canadian populations, for example. The list is incomplete; it is meant only to illustrate a unity of purpose in the diversity of resources.

To maintain repositories and data bases, there must be budgets. NIH had to withdraw support when the Yale human-genome resource outgrew its status as a pilot study project. Howard Hughes Medical Institute stepped in, sought and obtained a consensus from the scientific community, and undertook support of an international human genome–mapping resource (Lewin 1986). The NIH supports GenBank through a National Institute of General Medical Sciences contract. The NIH has a new section on Biological Models and Materials, with a director (Dr. James D. Willett) who is apparently sympathetic to taxonomy (Holden 1985) and is, we hope, authorized to fund related activities. The new mosaic of interest and funding is a welcome initiative, and in its diversity may be its strength. I hope that our own society will support these initiatives through the partcipation of its members and by letting its corporate views be known to the NIH, which requested the report from the National Academy of Sciences.

Genomics

In his Nobel lecture (Berg 1981), Paul Berg implied that any successful approach to an understanding of genetic disease would require knowledge of the molecular anatomy, physiology, and biochemistry of the human genome. This would be the knowledge base from which every physician could develop genetic thinking about human disease (Scriver 1984*a*, 1984*b*). Human geneticists use mutations to dissect determinants of homeostasis, and from these, among other approaches, we are developing a neo-Vesalian anatomy of our DNA. The new enterprise has a name: genomics.[4] The goal of the enterprise is an atlas and dictionary of expressed chromosomal loci and markers, a complete directory of informative probes for normal variant alleles (Scriver 1985; McKusick 1986*b*)[5] with associated multipoint linkage maps (White et al. 1985) designating the linear order and physical distances between assignments. The human map will contain Mendelian loci and markers, physical distances and order, restriction sites, and recombination frequencies on male and female

[4] The neologism "genomics" is attributed to Tom Roderick (Jackson Laboratory) and Victor McKusick (Johns Hopkins Hospital) among others; it was adopted in 1986 for the name of a new journal from Academic Press.

[5] McKusick's catalogs of Mendelian inheritance in man contain "low resolution" maps of the chromosomal assignments of loci; updating is maintained by a newsletter between editions of *Mendelian Inheritance in Man*. Updated maps are also published periodically, following the biannual workshops, in the journals *Clinical Genetics* and *Cytogenetics and Cell Genetics*.

chromosomes; it will have comparisons with the mouse map and others. The McKusick catalogs of Mendelian variation in man, generated largely by observant clinicians, record thousands of alleles both rare and polymorphic, giving insight into the ways in which the whole organism is programmed to work. Our need for cloned probes to identify loci and alleles is served by the directories and repositories mentioned earlier. In due course the atlas will encompass nucleotide sequences, certainly for expressed DNA and adjacent regions and eventually perhaps for the whole genome (or most of it). There has been some controversy as to whether our first priority is to map or to sequence the human genome (Lewin 1986).[6] (It is a rather sterile controversy about the time that it will take and its cost.) We can do both, simultaneously and judiciously. The ultimate challenge is to decide whether we can have the private linear maps that characterize every individual human—their DNA signatures, as it were—or whether we will settle for public probability maps of locations and sequences.

Mapping the human genome, to establish the corresponding normal and morbid anatomies, has been under way for years (McKusick and Ruddle 1977; McKusick 1986*b*). Its pace was accelerated by molecular methods and the development of chromosome sorting and ordered cosmid maps. The human genome contains $\sim 3 \times 10^9$ bp organized in 22 sets of autosomal chromosomes and one set of sex chromosomes in the nucleus, as well as one set of chromosomes in the mitochondria, and has about 10^5 coding regions accommodated by somewhere between 1% and 10% of our DNA. A saturated genetic and physical map of human loci and markers is attainable with time and commitment. For comparison, the genome of *Caenorhabditis elegans* is $\sim 8 \times 10^7$ bp, a size that would include many individual human chromosomes. A physical map comprising 860 clusters of clones, from 35 to 350 kb long, with contiguous nucleotide sequences (contigs) containing known loci (genetic map), has been characterized for 60% of the *C. elegans* genome (Coulson et al. 1986).

Sequencing of the human nuclear genome begins with the genes of greatest interest to individual investigators willing to make the effort; segments for which there are cDNA clones are likely to be most attractive initially. The work has both basic and applied significance. When the nucleotide sequences associated with diseases are known, the appropriate oligonucleotide probes and the longer single-strand probes that form heteroduplexes of DNA and RNA-DNA can be designed, along with the various separations of fragments, as diagnostic tools.[7]

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[6] The year 1986 witnessed geneticists (Dulbecco, R. 1986. Science **231**:1055–1056) and others proposing and debating the relative merits of "big" biological science (i.e., sequencing the whole human genome in a coordinated effort as a finite project) vs. continuing to do business in the accustomed matter (i.e., a random quasi-collaborative effort to map and sequence the genome according to the interests of the individual investigators). The debate was widely reported and commented on (see, e.g., Lewin, R. 1986. Science **232**:1598–1600; Gall, J. G. 1986. Science **233**: 1367–1368; Newmark, P. 1986. Nature **323**:291; and The Economist [May 24, 1986], p. 87).

[7] Techniques for analysis of DNA evolve steadily. An informed discussion of them was published by the U.S. Congress, Office of Technology Assessment, in September 1986: *Technologies for Detecting Heritable Mutations in Human Beings*. OTA-H-298 (Government Printing Office, Washington, D.C.).

Some say that mapping and sequencing will be expensive. Climbing mountains is also difficult and expensive; but the equipment gets better, the determination gets greater, and the expeditions get funded one by one; there is no mountain over 8,000 m on Earth that has not been climbed, and all 14 such mountains in the Himalayan range have been climbed by one committed man.[8] Human genomics is like mountain climbing; we will do it because the challenge is there—but also for its benefits, which are probably easier to predict than those of mountaineering. Vesalius influenced not only human biology and medicine but the sculpture and painting of our culture, and we take that for granted now (Saunders and O'Malley 1973). Our grandchildren will reap the benefits of our own neo-Vesalian enterprise, and it will be high praise if they do take them for granted. Whatever this society can do to facilitate the work will be worthwhile.

HOMEOSTASIS

The next five sentences are axioms or near axioms. Genetic loci are determinants of properties of the whole organism in various environments. Organization of loci in some yet ill-perceived hierarchical order in time and space influences the becoming and the being of the organism in its normal environment. Loci determine the properties of homeostatic systems and their homing values or central tendencies. Evolutionary experiments with genes and their properties may be conserved or lost by selection or chance. Cassettes of conserved DNA can be passed on, shuffled, amplified, and diffused through populations.

The following are generalities. It is important and interesting to know the parts of organisms and their properties. There are two ways to do this. One is to isolate the parts, move them around, make them work, and study their properties in a controlled system. When biochemists put the components into closed systems, they study the parts in vitro, which is not the same as in vivo et situ. When geneticists put a reductive determinant of one open system into a new one and study its properties, they are not then doing so in the old in vivo et situ hierarchy.

The second way is to study the whole organism, to use its emergent property in an attempt to understand how the components work together, and to capitalize on variation to observe how change in a part affects homeostasis of the whole. Measurements of the general impact of Mendelian diseases on biological parameters in man and the efficacy of treatment for such diseases are examples of this approach (Costa et al. 1985; Hayes et al. 1985). Garrod, the physician and colleague of Hopkins the biochemist, was among the first to use the second approach.

Garrod's first postulate of chemical individuality (Garrod 1909) was derived from his observations on persons with inborn errors of metabolism. He insisted that such persons were only the most obvious outliers in a general scheme

[8] Reinhold Messner used modern mountaineering methods, physiological adaptation, and a business flair to climb all the big mountains himself in the past decade (The Economist [November 1, 1986], p. 51).

(Garrod 1902). He went on to develop his second postulate—that of inherited susceptibility to disease under various conditions. The rubric for this idea was the title of his second book: *The Inborn Factors in Disease* (Garrod 1931).

Nearly everyone working in human genetics now uses Garrod's first postulate. Mendelian variants help us to develop catalogs and map the genome (McKusick 1986*a*). They give us an enormous array of variant phenotypes to study. For example, the Dallas group studied the J.D. mutation, which causes deficient low-density-lipoprotein receptor activity and hypercholesterolemia (Davis et al. 1986). They found a single amino acid substitution in the cytoplasmic domain of the receptor associated with a failure of the receptor to aggregate in the coated pits of the plasma membrane. Then they used site-directed mutagenesis on the normal allele to prove that the normal cytoplasmic domain had a property necessary for location of the receptor in coated pits. An elegant problem and a satisfying experiment.

Garrod's second postulate has been less well received by those of our medical colleagues who must deal with cause and treatment of disease, probably because it has been more difficult to verify, less overt in its evidence, and perhaps because very few of us have read his second book—even if we know about it. But molecular genetics, with its ability to display genotype, could at least put some of our genetic susceptibility into perspective and bring about enlightened interactions between epidemiologists and geneticists, among others. The second postulate will convert epidemiological thinking about sick populations into new thinking about sick individuals within those populations (Rose 1985) by addressing the question, Why does this patient have this disease, now (Scriver 1984*a*)? It is a question that medical geneticists ask naturally. It is very different from the physician's usual question: What is the diagnosis, and what is the treatment of my patient's disease? Or the epidemiologist's question: How do I explain the incidence of this disease? The geneticist's question addresses both ultimate (meaning genetic) and proximate (meaning secular) causes of disease and its pathogenesis, and it may anticipate forms of prevention. The physician's question considers the manifestations of dishomeostasis after the fact, when their costs already have been exacted.

Physicians are not usually taught to appreciate that genes propose and experiences dispose (Childs 1977). They are familiar with the public-health paradigm and its hypothesis that experiences can overwhelm homeostatic systems. Cause of disease here is proximate; therefore, physicians say, if one controls the experience one controls the disease. Much less familiar is the proposition that a variant genotype in an individual can undermine the network of homeostatic responses when proximate causes are at work. Specific persons get a particular disease in a particular circumstance, according to this way of thinking.

Physicians are chosen and trained to be good taxonomists of categorical phenotypes called diseases (for which there is still no logical, biologically based classification of cause). As a class, and according to my observations, physicians are usually uninterested in history. These characteristics may explain, in part, why physicians have trouble with genetics (which is a form of history),

need to know genetic principles and the associated medical examples, do not think about health and disease as the counterparts of homeostasis and dishomeostasis, and are not encouraged to believe that evolution gave mankind the genotypes that propose the homing values of homeostatic phenotypes (Childs 1974, 1977; Scriver 1984*b*).

Medicine, as a discipline with a point of view, has attempted recently to account for the continuation of disease in a better world by laying a large portion of the blame on life-style (Knowles 1977). This is a rather moral view of disease—yet one that accommodates some of our human characteristics that explain phenotype. It is not a profound biological view. However, because of the new insights that genetic technology can give us, genetics is making inroads on the medical mind; notice how the molecular explanations of categorical diseases are increasingly accepted for publication in the major medical journals. Garrod's outliers of the first postulate are becoming conventional medical wisdom in the treatment of not-so-rare diseases. Yet progress in accepting Garrod's second postulate is so much slower, and that is my worry. I am not advocating biological determinism as the only explanation of human variability and disease; we know about the excesses perpetrated in the name of determinism. I merely ask that it be considered as a real component of our imperfections and that we teach it to those who must treat them.

It seems so much more difficult to believe that a particular gene, which determines a component in a homeostatic network, contributes to the phenotype value of the total network; that all the genes conferring the property of the homeostatic matrix, acting together, set the threshold against which a variant in one of the components might put the whole network at risk and, under a particular circumstance, compromise homeostasis—to believe, in other words, in a physiological/genetic view of disease. It follows that genotype at one locus might be benign on one background genotype and harmful on another under more or less similar environmental circumstances, or that the risk of a potentially adverse circumstance is different for different people with the same single-gene variant.

Geneticists do not have great difficulty with this style of thinking; apparently, physicians do. You found this message acceptable last year when I presented a paper on the Hartnup phenotype in this context (Scriver et al. 1985). I have not had any success in selling that particular example to editors of medical journals. The Hartnup model is a paradigm for so-called multifactorial disease, but it is a difficult one. It is not categorical, and it does not satisfy physicians—or, more particularly, those who dictate styles of medical thinking.

OUR SOCIETY

The American Society of Human Genetics is an international social organism with a charter, a hierarchical structure, and parts. The basic unit is the member in all of her or his splendid variety: 220 members in 1948, just under 3,000 in late 1986. Members are loosely organized by subspecialty according to their various interests. There is a superstructure: a board of directors, officers, and numerous committees. The dues and other sources of income are a form of

energy maintaining the structure and dissipated effectively by it. The mitochondrial analogue is the executive committee and the now well-established administrative office and its excellent staff—an important development that arose from the concerns of two past presidents.

Emergence is a property of our society. As a whole, it has a peculiarity that might not be deduced from its components. It has a phenotype or, more precisely, two major phenotypes—perhaps more. One, easily recognized and well established, is scientific, reductive in nature, competitive, and successful—and visible as the excellent annual scientific program, our awards, and the journal. The other is social; apparent in the membership directory, much of our committees' work, and the Guide to Training Programs; and, by comparison with the scientific phenotype, holistic. In this second form, I think, we are still underdeveloped, a point of view expressed 6 years ago by a former president (Rosenberg 1981). He opined that we were, at that time, a closet society in our social phenotype. Since then, we have moved more into the light. Yet, if other organizations and individuals still choose not to consult us for our views on issues, we cannot make them do so. But we can help them to notice us by making our presence better known. This does not mean that we have the correct solution for any specific social problem in human genetics, but we do have views that might be expressed and debated in public to the benefit of the societies in which we live. One way to be visible is to publish reliable statements on issues that matter to society at large. Not many of these have been published by the society. We are not yet fully emergent in that aspect.

During the past year there were two initiatives to produce such documents. One was a policy statement concerning the maternal serum alpha-fetoprotein test; the other concerned the merits of teaching genetics better in medical schools and to medical graduates—to deal with Garrod's second postulate, among other things. Past presidents often alluded to the latter theme in their published addresses.[9] We had difficulty moving from intent to achievement in both areas this year. These difficulties are not explained by a failure of effort or commitment by members. Many hours were devoted by many members to the drafting, reviewing, and revision of the texts for both statements. Our difficulties lie, I sense, in a deficiency of structure in this area—perhaps also in an unwillingness by members to trust the judgment of our delegates in these activities. We have had too little mechanism to facilitate this difficult and important collective exercise, too few staff to maintain the momentum, and an inadequate commitment of budget to convene the committees for those vital moments of interaction and creativity that produce data and ideas for the preparation of reliable statements. If the society believes that the time has come for it to take thoughtful positions on public issues in human genetics, this emergent property will require a larger commitment of both effort and money, from the members and from the corporate structure.

[9] At least four presidential addresses addressed the education of physicians in genetic principles and methods of research: Herndon, C. N. 1956. Am. J. Hum. Genet. **8**:1–7; Childs. B. 1977. Am. J. Hum. Genet. **29**:1–13; Motulsky, A. G. 1978. Am. J. Hum. Genet. **30**:123–131; and Littlefield, J. W. 1984. Am. J. Hum. Genet. **36**:731–735.

What phenotypes do we wish for the society? What we attain rests with decisions of the units. I repeat the challenge. Do we continue to be a somewhat reductive and closeted phenomenon, or do we emerge as a major organism on behalf of human genetics and its associated issues in the world of today? Two aphorisms by Immanuel Kant can focus our minds. The first: *What can I know?* It is a reductive question. We answer this question rather well, year by year, in our scientific mode. The second: *With that knowledge what ought I do?* (or, if you were raised on Bunyan's *Pilgrim's Progress, What shall I do?*). It is a rather physiological question. We are learning better to answer it in our social mode. But we have more to do. In this phenotype, we are still developing.

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